REMARKS

Claims 1-10, 20, 25-27 and 29 were previously pending in this application. By this amendment, claims 1, 2, 4, 7-10, 20, and 25 have been amended.

Claims 1 and 2 have been amended to correct the antecedent basis for limitations in the claims and to clarify the relationship between the detection steps and the coding region/gene identification.

Claim 4 was amended to correct a minor typographical error in the reference number of a YAC clone.

Claim 7 has been amended so that the language in the final step in the claim corresponds to the language in the preamble. Support for the amendment can be found at least in the claim as originally filed. Claim 7 has also been amended to clarify the antecedent basis for claims 9 and 10.

Claim 8 has been amended to reflect that the claim is to the use of a YAC clone that includes a portion of human chromosome 18q disposed between the specified markers, rather than any YAC clone comprising triplet repeats. Support for the claim can be found at least in the specification as filed at Experimental 2, and in claim 8 as originally filed.

Claim 20 has been amended to clarify the identity of the probe as a cDNA encoded by a coding region/gene identified as set forth in claim 7. Support for the amendment can be found at least in claims 7, 17-20 as originally filed. Claim 20 has also been amended to clarify that a control individual is an individual who is not affected by a mood disorder or related disorder and does not have a family history of mood disorders. Support for the amendment can be found in the specification as filed at least at page 10, lines 32-35.

Claim 25 has been amended to clarify the claim language. Support for the amendment can be found in the specification as filed at least at page 10, lines 32-35.

As a result claims 1-10, 20, 25-27, and 29 are pending for examination with claims 1, 2, 7, 8, and 25 being independent claims.

The specification has been amended to remove the addresses added in the previous amendment and to include web addresses and not hyperlinks. Support for the amendment can be

found at least in the amended paragraphs of the application as filed. No new matter has been added.

Oath/Declaration

The Examiner indicated that the priority claim present in the original Declaration of the Inventors was incorrect. Applicants submit herewith a new Declaration executed by all of the inventors to correct the priority claim.

Specification

As suggested by the Examiner at page 4 of the Office Action, Applicants have deleted the added names/addresses and replaced them with the previously recited web addresses lacking the previously recited http:// so as to provide web addresses rather than embedded hyperlinks.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-10, 20, 25-27, and 29 under 35 U.S.C. §112, first paragraph as not enabled. Applicants respectfully traverse the rejection.

The Examiner maintains that the teaching of the specification does not support an association between mood disorder and the region of chromosome 18q recited in the claims. The Examiner cites the teaching in the specification that "a LOD score of 3 (or likelihood ratio of 1000 or greater) is taken as significant statistical evidence for linkage" and the prior art reference of Kahl (Dictionary of Gene Technology) as suggesting that a LOD score of 1.34 is not indicative of linkage.

As set forth in the previous Office Action response, Applicants submit that the association between the region of chromosome 18q and mood disorder is supported in the specification at page 4, lines 10 to 22, which describes a study in which LOD score analysis was performed on family MAD 31, a Belgian family of a BPII proband. In support of Applicants' position, Applicants include herewith copies of the Freimer et al and Coon et al references for the Examiner's review.

Additionally, Applicants respectfully submit that the requirement for the LOD score to be 3 or greater in order to provide significant statistical evidence for linkage, as taught by Kahl, applies only in studies where the LOD score was obtained using a full genome scan. However, in the present case Applicants did not perform a complete genome scan of family MAD 31, but rather a fragment of chromosome 18 was scanned using STR markers in a multipoint linkage analysis. In such a multipoint linkage analysis, the criteria of Kahl *et al.*, requiring a threshold LOD score of 3 for significant linkage, do not apply. Instead, for multipoint analysis the criteria of Lander and Kruglyak, (Nature Genetics, 1995, 11(3); 241-247, copy enclosed) are applicable.

According to the criteria of Lander and Kruglyak a LOD score of 1.2 (p=0.01) is sufficient to indicate a significant association in multipoint linkage analysis. Applicants submit that this is supported at page 245 of this reference, left-hand column, fourth paragraph, where it is stated that "because one is searching over an interval, there is a multiple testing problem writ small: the chance of finding a P value of 0.05 somewhere within a 20 cM interval is greater than 5%. It turns out that a point wise P value of 0.01 is needed for an interval-wide significance level of 5%. Accordingly, P = 0.01 should be required to declare confirmation at the 5% level" to confirm linkage. Thus, in the context of a multipoint linkage analysis a LOD score of 1.34 should be treated as an indication of linkage. Applicants respectfully assert that the criteria of Lander and Kruglyak are accepted in the art in the context of multipoint analysis and have been extensively cited by others.

In addition, should it be required, Applicants can provide a Declaration in support of the assertion that the LOD score set forth in the specification as filed is statistically significant evidence of linkage.

Additionally, as discussed in the previous Office Action response, Applicants submit that the association between the region of chromosome 18q and mood disorder is supported in the specification at page 4, lines 10 to 22, which describes a study in which LOD score analysis was performed on family MAD 31, a Belgian family of a BPII proband. In support of Applicants' position, Applicants include herewith copies of the Freimer et al and Coon et al references for the Examiner's review.

With regard to the disclosures of the Goossens reference, the inventors acknowledge that Goossens *et al.* teach that none of the specific triplet repeats examined in that study are significantly associated with mood disorder or form part of a gene associated with mood disorder. However, the triplet repeats themselves form only a very small part of the entire chromosomal region disposed between markers D18S86 and D18S979 and the fact that these repeats do not show a significant association when considered in isolation does not affect the significance of the association taken over the entire region.

By examining associations with the individual triplet repeats, Goossens *et al.* effectively tried to narrow down the region of linkage on chromosome 18 from the large region between markers D18S86 and D18S979 to the very small regions covered by the triplet repeats. Their results indicated that the peak of linkage does not occur within any of the triplets, so it must occur elsewhere within the large region between markers D18S86 and D18S979. Overall, the region between markers D18S86 and D18S979 is still significantly associated with bipolar disorder. Applicants can provide the Examiner with a Declaration in support of this conclusion if required.

The Examiner noted that the data reported in the specification (from the MAD31 family) does not provide evidence of a significant association with any mood disorder, and therefore the claims are not enabled for this additional reason.

Applicant respectfully notes that the claims do not pertain to <u>any</u> mood disorder. Rather, the claims are limited to identifying human coding regions/genes relevant to mood disorders by analyzing and detecting differences in an 8.9 cM region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979 (claims 1, 25 and claims dependent therefrom), or a YAC clone comprising a portion of human chromosome 18q disposed between polymorphic markers D18S60 and D18S61 (claims 2, 8 and claims dependent therefrom). Thus, the claims clearly are limited by the specific regions of human chromosome 18q as recited in the claims. The claims as limited to these regions are fully enabled.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 1-10, 20, 25-27, and 29 under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 4-5 under 35 U.S.C. §112, first paragraph as lacking adequate written description. Applicants respectfully traverse the rejection.

Applicants provide herewith a copy of a page from the CEPH website (www.cephb.fr/ceph_yac.html), last updated June 27,1996, which confirms that as of this date the entire collection of CEPH YAC clones was available from a number of sources, including the MRC geneservice based in Cambridge, UK and the Whitehead Institute in the U.S. Applicants submit that this evidence is sufficient to demonstrate that at the time of filing one or ordinary skill in the art would be able to obtain any of the YAC clones referred to in claims 4 and 5.

In addition, several pages from the website of the MRC geneservice (www.hgmp.mrc.ac.uk/geneservice) are provided. These pages indicate the current availability of the CEPH YAC clones from MRC geneservice. The obtainability of the YAC clones from MRC geneservice indicates that they are currently available.

Applicants also provide copies of the printouts of several webpages having information on the YAC clones recited in claims 4 and 5, from the YAC information database formerly hosted on the Whitehead Institute's website and now hosted on the Broad Institute's website (www.broad.mit.edu/cgi-bin/contig/yac_info). According to the website, the Broad Institute is "a partnership among MIT, Harvard and affiliated hospitals and the Whitehead Institute for Biomedical Research. Its mission is to create the tools for genomic medicine and make them freely available to the world and to pioneer their application to the study and treatment of disease."

From the foregoing, it is clear that the YAC clones are known and readily available. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 4 and 5 under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-10, 20, 25-27, and 29 under 35 U.S.C. §112, second paragraph as being indefinite.

The Examiner has rejected claims 1 and 6 and 2-5 as indefinite over the recitation of the limitation "the equivalent regions of DNA from a person afflicted with a mood disorder or a related disorder" in claim 1 as having insufficient antecedent basis for this limitation. Applicants have amended the claim to read "an equivalent region..." and submit that this corrects the inadvertent error in antecedent basis.

The Examiner has rejected claims 1 and 6 and 2-5 as indefinite over the recitation of the terms "equivalent regions of DNA" in claims 1 and 2. Applicant has amended claims 1 and 2 to read "equivalent region of DNA" and submit that based on the art-recognized meaning of an equivalent DNA region, the meaning of this phrase would be clear to one of ordinary skill in the art. Applicants assert that one of ordinary skill in the art would know that an equivalent region means the region occupying the equivalent physical position on chromosome 18q, or the same genetic locus, in the genome of the disease-afflicted subject. One of ordinary skill would know that the term "equivalent" has a similar meaning to the term "homologous" as used when referring to the degree of correspondence between homologous chromosomes from individuals of the same species. Thus, Applicants submit that the term "equivalent" as used herein in the context of gene comparisons is clear.

The Examiner further states that it is unclear whether the "identifying" and "detecting" steps of claims 1 and 2 require the same or different "equivalent regions" and requests clarification. Applicants submit that for any given region of the human genome, for example a fragment of a human chromosome 18q cloned into a vector, there will be only one "equivalent region" in the genome of a human subject, or two copies of the region on homologous chromosomes. Because of the amendment to the claim correcting the antecedent basis for the "equivalent region", Applicants believe that based on the understanding of the human genome and the antecedent relationships present in the claim, it is clear that the "equivalent region" would be the same for both the identifying and detecting steps.

The Examiner has rejected claims 1 and 6 and 2-5 as indefinite over the recitation of the phrase "wherein a difference in the coding regions/genes is an indication that the coding region/gene or mutated or polymorphic variant thereof is associated with the mood disorder or related disorder" in claims 1 and 2.

The Examiner indicates there is a lack of antecedent basis for the recitation "the coding region/gene or mutated or polymorphic variant thereof". Applicants have amended claims 1 and 2 to correct the antecedent basis and believe the amendment addressed this basis for the rejection.

The Examiner also expresses uncertainty as to why one would expect a version of a gene that differs from that present in an individual with a disorder to be associated with the disorder (as opposed to the version that is present in the individual with the disorder). Applicants respectfully assert that the method covered by claim 1 involves first identifying a potential a coding region or gene in the region of chromosome 18q bounded by the markers D18S68 and D18S979. This may be carried out using cloned fragments of genomic DNA contained in suitable vectors, such as YACs, but it could also be done *in silico* using information available from the human genome project. A coding region or gene identified as a result of this analysis, which is a wild-type allele, is then compared with the "equivalent" or homologous gene or coding region in an individual with mood disorder. If differences are found to exist between the wild-type allelic version of the gene and the version present in mood disorder patients then this indicates that the coding region or gene (meaning the genomic locus) is associated with mood disorder. The Examiner is correct in that it is most likely the allelic version of the gene present in the mood disorder patient that is functional or causative of disease, and not the wild-type version, but submit that the method does identify the wild-type coding region or gene that is associated with the mood disorder. Thus, alterations in the identified wild-type version results in the disorder, identifying the coding region or gene associated with the disorder. Applicants have amended claims 1 and 2 to clarify that if a difference is detected between the coding region/gene and the equivalent region, it means that the coding region/gene is a region associated with the disorder.

The Examiner additionally requests clarification of the use of the term "detecting" in the final step of claims 1 and 2 and the term "identifying" in the preamble of claims 1 and 2. Applicants have amended claims 1 and 2 to recite that a difference in the coding region/gene *identifies* the coding region/gene or mutated or polymorphic variant thereof as associated with the mood disorder or related disorder. Applicants respectfully submit that this amendment clarifies the claims and obviates the basis of the rejection.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-6 under 35 U.S.C. §112, second paragraph in view of the arguments and amendments made herein.

The Examiner has rejected claims 7, 9-10, and 20 under 35 U.S.C. §112, second paragraph as indefinite. Applicants have amended claim 7 to indicate that detection of the presence of trinucleotide repeats in a region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979 *identifies* the presence of a human coding region/gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder. Applicants assert that the phrase "identify the presence of" means to detect that a coding region/gene associated with a mood disorder or related disorder is present in the region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 7, 9, 10 and 20 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claim 8 under 35 U.S.C. §112, second paragraph as indefinite.

The Examiner contends that the phrase "equivalent region of DNA" is indefinite. Applicants respectfully traverse the rejection. Given the claim language, it is clear that the "equivalent region" is that region corresponding to the sequence identified in the method (i.e., between the markers D18S60 and D18S61 and containing trinucleotide repeats).

The Examiner also rejected the claim as indefinite over the recitation "wherein a difference in the sequence flanking the triplet repeats and the DNA from the afflicted person is

an indication of a human gene or mutated or polymorphic variant thereof that is associated with the mood disorder or related disorder." Applicants have amended the claim to reflect the scope of the claim as originally filed. The claim is drawn to a method of identifying at least one human coding region/gene, including mutated or polymorphic variants thereof, which is associated with a mood disorder or related disorder that includes fragmentation of a YAC clone as defined in claim 2 and the detection of nucleotide triplet repeats. Thus, the claim includes steps of transforming a YAC clone with a sequence that includes a portion of human chromosome 18q between markers D18S60 and D18S61, identifying a transformed clone, determining the presence of trinucleotide repeats in the region between the markers and comparing that determination to the sequence between the markers in an equivalent sequence from a subject with a mood disorder or related disorder. If there is difference between the trinucleotide repeat determination in the cloned sequence compared to the sequence from the subject with a mood disorder or related disorder, it means that the region between the markers contains a coding region/gene that is associated with the mood disorder or related disorder. As described above, because the cloned sequence is the wild-type sequence, the method allows one to identify the presence of a coding region/gene on 18q between markers D18S60 and D18S61 that is associated with mood disorder or related disorder.

Based on the amendments to claim 8, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 8 under 35 U.S.C. §112, second paragraph.

The Examiner rejected claims 9 and 10 as indefinite over the recitation of the limitation "said triplet repeat" in claim 9 as lacking antecedent basis in claim 7. Claim 7 has been amended to clarify the antecedent basis for claims 9 and 10. Applicants submit that the amendment to claim 7 obviates the basis for the rejection of claims 9 and 10 as indefinite.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 9 and 10 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claim 20 under 35 U.S.C. §112, second paragraph as indefinite. Applicants have amended claim 20 to clarify that the probe encompassed by the claim is a cDNA encoded by a coding region/gene identified as set forth in claim 7.

The Examiner also states that the meaning of the control individual is unclear. Applicants have amended claim 20 to clarify that the control is an individual who is not affected by a mood disorder or related disorder and does not have a family history of mood disorders.

Applicants submit that the amendments to claim 20 obviate the rejection and requests the Examiner withdraw the rejection of claim 20 under 35 U.S.C. §112, second paragraph.

The Examiner has rejected claims 25-27 and 29 under 35 U.S.C. §112, second paragraph as indefinite. Applicants have amended claim 25 to clarify the steps of the method as including the comparison of the DNA polymorphism of a sample from an individual to a sample from a control individual who is not affected by a mood disorder or related disorder and does not have a family history of mood disorders and a sample from an individual, in order to determine the susceptibility of the individual to a mood disorder or related disorder. The claim as amended sets out the steps that include obtaining samples from the individual and control individual, amplifying a nucleotide sequence comprised in the sequences shown in Figure 15a, (SEQ ID NO:12), determining the presence of a DNA polymorphism in the amplified products from the DNA sample and the sample from the control individual, and comparing the results of the amplification reaction for the individual and for the control individual; wherein the presence of an amplified product that includes a DNA polymorphism associated with a mood disorder or related disorder in a region of chromosome 18q disposed between polymorphic markers D18S68 and D18S979 that is different in the individual sample than in the sample from the control individual is an indication of the presence of a susceptibility to a mood disorder or related disorder of said individual. Applicants submit that the claim as amended clearly indicates how the steps performed relate to the identification of the susceptibility of an individual to a mood disorder or related disorder.

The Examiner also rejected claims 25-27 and 29 as indefinite over the recitation of "related disorder of said individual". Applicants are uncertain as to the basis for the rejection

because the full phrase in claim 25 is "mood disorder or related disorder of said individual", which phrase clearly refers back to the individual recited in the preamble.

Applicants submit that the amendment of claim 25 obviates the rejection and request that the Examiner withdraw the rejection of claims 25-27, and 29, under 35 U.S.C. §112, second paragraph.

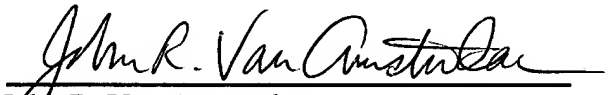
The Examiner has rejected claim 29 under 35 U.S.C. §112, second paragraph as indefinite because there is insufficient antecedent basis for the limitation "said nucleotide sequence to be amplified". The phrase does find antecedent basis in part b) of claim 25: "providing primers suitable for the amplification of a nucleotide sequence". Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 29 made under 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' representative at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Christine Van Broeckhoven et al., Applicant

By: 

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